Benefits of Caffeine on Health

Subjects: Nutrition & Dietetics

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Caffeine is a naturally occurring alkaloid found in various plants. It acts as a stimulant, antioxidant, anti-inflammatory, and even an aid in pain management, and is found in several over-the-counter medications. This naturally derived bioactive compound is the best-known ingredient in coffee and other beverages, such as tea, soft drinks, and energy drinks, and is widely consumed worldwide. Caffeine is probably the most commonly ingested psychoactive substance in the world, found mainly in coffee, soft drinks, tea, cocoa and chocolate-like products, yerba matte leaves, guarana berries, and some pharmaceuticals. It is rapidly absorbed and distributed in all human tissues, reaching maximum plasma concentrations 30–120 min after oral intake.

Keywords: caffeine ; health benefits ; athletic effects

1. Cancer

Cancer is one of the leading causes of death worldwide. It was estimated that in 2020, there were 19.3 million cancer cases, which resulted in 10.0 million cancer deaths [1][2]. By 2030, it is estimated that over 22 million people will develop cancer [2][3]. In addition, cancer is responsible for a significant economic burden on both the health care system and patients [3].

As early as 2000, Hanahan and Weinberg defined the key features (i.e., “hallmarks of cancer”) that describe the characteristics necessary to promote cancer growth and metastasis. These hallmarks are self-sufficiency in growth signals, insensitivity to antiproliferative signals, resistance to apoptosis, limitless replicative potential, the induction of angiogenesis, and the activation of tissue invasion and metastasis [4]. In 2011, the authors revised the original hallmarks and added two more cancer-promoting features (genomic instability and tumor-promoting inflammation) and two more hallmarks (deregulation of cellular energetics and avoidance of immune destruction) [5]. As the understanding of cancer underlying mechanisms of progression has grown, as have the available experimental and computational tools; early in 2022, Hanahan reviewed the previously discussed features and included new additional features of cancer, namely, (i) phenotypic plasticity, (ii) non mutational epigenic reprogramming, (iii) polymorphic microbiomes, and (iv) senescent cells [6].

The role of coffee components in suppressing some of the cancer hallmarks defined by Hanahan and Weinberg [7][8] has been reviewed by Gaascht et al. and Cadóna et al., while other authors have fully elucidated the effect of caffeine on the cell cycle [9]. Caffeine anticancer activity has been widely studied [10], and the below-stated findings demonstrate the capacity of caffeine to overcome some of the cancer-promoting hallmarks, such as resistance to cell death and cellular senescence, that play an important role in cancer progression [6]. Further, several works state that caffeine may induce apoptosis through numerous pathways, such as p-53-dependent and -independent, phosphatase and tensin homolog, PI3K/protein kinase B (AKT), and mammalian target of rapamycin (mTOR) pathways [11].

El Far et al. studied the effect of caffeine and other natural substances on the senescent cells of colon and breast cancers. After inducing senescence with doxorubicin, the cells were treated with various doses of caffeine (0, 5, 10, 15, 20, 30, 40, 50, and 60 mM). The IC_{50} of caffeine against doxorubicin-treated HCT116 and MCF7 cells was 13.36 ± 2.29 mM and 17.67 ± 3.98 mM, respectively. The authors also examined caffeine-induced apoptosis in both senescent and proliferative cells. At concentrations of 10 and 15 mM, caffeine induced a significant increase in apoptosis in senescent HTC116 cells, and at concentrations of 5, 10, and 15 mM in senescent MCF7 cells compared with proliferative cells [11]. In another study, Machado et al. evaluated the effect of caffeine on two breast cancer cell lines (MCF-7 and MDA-MB-231). The results showed that caffeine at a concentration of 2.5 mM and 5 mM for MCF-7 and MDA-MB-231, respectively, reduced cell viability and induced apoptosis [12]. The antitumoral effects of caffeine were studied in diverse cancer in vitro models, such as glioblastoma, melanoma, and pancreatic and lung cancers [13][14][15].

The antitumoral effects of caffeine have also been evaluated in in vivo tumor models. Venkata Charan Tej and collaborators investigated the effect of caffeine on the carcinogen-induced tumor model of fibrosarcoma. After 250 days of 3-MCA inoculation, there was a dose-dependent decrease in the tumor incidence and growth rate in the groups treated with caffeine (1.030, 2.060, and 4.120 mM) [16]. The anti-tumoral effect of caffeine was related to its action on cytotoxic T lymphocytes. On one hand, caffeine led to a higher percentage of cytotoxic T cells in the tumor, and on the other hand, it decreased the expression of programmed cell death protein 1 (PD-1) on these cells. In addition, it also increased the levels of pro-inflammatory cytokines such as TNF-α and IFN-γ. These results are in line with the previously known inhibitory effect of caffeine on the adenosine-A2a receptor pathway [17], which is one of the immunosuppressive pathways involved in cancer [18][19]. This capacity of caffeine to modulate the immune system in the tumor surroundings alters another important hallmark (i.e., the ability to avoid immune destruction). The modulation of the PD-1, an important immune checkpoint, and consequent enhancement of the T cell responses can exert an antitumor effect. In fact, the inhibitors of this protein are one of the immunotherapies approved by the FDA [20].

The therapeutic effect of caffeine was also demonstrated for renal carcinoma. Xu et al. showed, through in silico studies, that caffeine is able to bind to glucose-6-phosphate dehydrogenase (G6PDH), which is considered a biomarker and potential therapeutic target for this type of cancer. Consistent with the above results, in this study, the use of caffeine at concentrations of up to 0.016 mM for in vitro studies and 60 and 120 mg/kg/day for in vivo studies decreased the viability and proliferation of ACHN and 786-O cancer cells both in vitro and in vivo [19]. G6PDH is an important target in cancer given that is normally upregulated in different cancers and its dysregulation can provide valuable conditions for cancer progression [21]. Further, it also has an important role in maintaining the redox balance and biosynthesis of nucleotides and lipids, which is part of another cancer hallmark (i.e., reprogramming cellular metabolism) [22].

As previously mentioned, caffeine has also been tested in combination with other drugs in order to potentiate the antitumoral effect [23][24][25][26]. Higuchi et al. evaluated the efficacy of oral recombinant methioninase (o-rMETase) in combination with caffeine and doxorubicin in an orthotopic xenograft mouse model of synovial sarcoma. After two weeks of treatment, the group treated with the combinatorial treatment was able to induce tumor regression. According to the authors, this can be explained by the ability of caffeine to induce mitotic catastrophe [27]. Other examples of caffeine combination with different drugs are depicted in **Table 1**.

Table 1. Overview of the latest research regarding caffeine anti-cancer activity.

Target Cancer	Study Type	Model	Caffeine Exposure	Result	Reference
Breast	**In vitro**	**MCF-7 and MDA-MB-231cells**	**1–10 mM**	**Caffeine reduced the cell viability in concentrations greater than 2.5 mM for MCF7 and for 5 and 10 mM for MDA-MB-231 cell lines. At the latter concentrations, caffeine induces apoptosis and necrosis in both cell lines.**	**[12]**
Breast	**In vitro**	**MDA-MB-231, MCF7 and MCF10A cells**	**0.000125 mM**	**After MDA-MB-231 and MCF7 cells' treatment with caffeine, there was a change in metabolism towards respiratory-chain phosphorylation with low ratio of free to bound NADH. In combination with cisplatin, there was a decrease in viability and preference of cancer cells over normal breast cells.**	**[28]**
Breast and colon	**In vitro**	**HCT116 and MCF7 cells**	**0–60 mM**	**Apoptosis increased in both proliferative and senescent cells after treatment with caffeine at a concentration of 15 mM.**	**[11]**
Carcinoma squamous cells	**In vitro**	**HN5 and KYSE30 cells**	**0.5–70 mM**	**Caffeine at concentrations of 20, 50, and 70 mM presented an inhibitory effect and decreased the proliferation rate of both cell lines.**	**[29]**

Target Cancer	Study Type	Model	Caffeine Exposure	Result	Reference
Endometrial	In vitro	RL95-2, HEC-1-A and KLE cells	0–40 mM	Therapeutic concentration of cisplatin decreased from 4.1 to 1.1 μM and from 163 to 6.6 μM, with caffeine concentrations of 1.1 and 5.3 mM, respectively.	[25]
Glioblastoma multiforme	In vitro	Human GBM and U87-MG cells	1 mM	Pre-treatment of cells with caffeine followed by combined treatment of temozolomide and caffeine significantly decreased cell viability compared to the other groups.	[24]
Glioblastoma multiforme	In vitro	Human GBM, U87MG and T98G 101 cells	0.5–10 mM	In both cell lines, caffeine at 2.5 mM was able to reduce cellular viability, which was more pronounced under hypoxia.	[14]
Lung	In vitro	NCI-H23 and MLC15 cells	0–0.5 mM	After of NCl-H23 cells' treatment with 0.25 and 0.50 mM caffeine, the size of colonies decreased by 78.1% and 63.9%, respectively. In addition, caffeine induced cell arrest in the G0/G1 phase, reduced the S phase of the cell cycle, and suppressed cell invasion.	[30]
Melanoma	In vitro	Normal human melanocytes COLO829 and C32 cells	100–1000 mM	The results showed the ability of caffeine to reduce the viability of COLO829 and C32 cells by 5–35% and 1–16%, respectively. In addition, it also led to a decrease in thiol degradation and pro-apoptotic effects and did not affect normal melanocytes cells.	[15]
Melanoma	In vitro	B16F10 cells	0.001–0.04 mM	Cells' pre-treatment with caffeine enhanced the cytotoxic effects induced by dacarbazine. In addition, caffeine increased oxidative stress in a dose-dependent manner.	[13]
Pancreatic ductal adenocarcinoma	In vitro	AsPC-1, BxPC-3, Capan-1, COLO-357, MiaPaCa-2, SU.86.86, PANC-1, and T3M4 pancreatic cancer cells	0.1, 0.2 mM	Caffeine enhanced cell death induced by 5-fluorouracil and gemcitabine, and also decreased the IC_{50} of both chemotherapeutic agents.	[26]
Prostate	In vitro	PC-3 cells	0.5 mM	Caffeine affected cell viability in a dose-dependent manner. Cell migration and invasion ability was more affected by the combination of atorvastatin and caffeine than by caffeine alone. The same was observed for the formation of tumor spheres.	[31]
Glioma	In vitro and in vivo	RT2 cells-induced glioma in male Fischer 344 inbred rat	100 mg/kg/day orally (2 weeks) plus temozolomide given once daily (5 days)	The combination of caffeine with temozolomide inhibited tumor growth compared to the control group.	[23]
Hepatocellular carcinoma	In vitro and in vivo	SMMC-7721 and Hep3 cell lines and Male BALB/c nude mice	0–32 mM (in vitro) 20 mg/kg/day injected IP every other day for (2 weeks)	Caffeine decreased the viability of both cell lines and had a synergistic effect with 5-fluorouracil. In addition, tumor growth was suppressed, and tumor weight was reduced in mice treated with caffeine alone or in combination with 5-fluorouracil.	[32]

Target Cancer	Study Type	Model	Caffeine Exposure	Result	Reference
Osteosarcoma, fibrosarcoma	In vitro and in vivo	HOS, HT1080 and LM8 cells and athymic nude mice	0.5 mM (in vitro) 100 mg/kg injected IP on days 2 to 4 to the treatment (1 week). The treatment was performed two times.	The combination of cisplatin and caffeine decreased cell viability compared with cisplatin alone. In vivo, after implantation of LM8 and HT1080 cells, the combination of cisplatin + caffeine decreased tumor volume and weight.	[33]
Pleomorphic rhabdomyosarcoma	In vitro and in vivo	RMS cells, Athymic nu/nu nude mice	0.5 and 1 mM (in vitro) 100 mg/kg/day injected IP daily (3 weeks)	Caffeine showed the ability to enhance the antiproliferative effects of valproic acid. In vivo, the group treated with caffeine and valproic acid showed a reduction in tumor volume compared to the control group. This was also confirmed in the group treated with *Salmonella typhimurium* A1 receptor in combination with caffeine and valproic acid.	[34]
Renal cell carcinoma	In silico, in vitro, and in vivo	ACHN and 786-O cells, and BALB/c nude mice	0–0.016 mM intragastrically administered for 34 consecutive days	The molecular docking studies demonstrated that caffeine was able to bind to G6PDH at the NADP+ binding site, which is a biomarker and potential therapeutic target for renal cell carcinoma. In addition, caffeine was able to decrease the viability and proliferation of both cell lines and in the in vivo studies.	[19]
Colorectal	In vivo and in silico	Swiss Webster mice	50 mg/kg/day, intragastrically 5 times a week (10 weeks)	Mice treated with caffeine alone or in combination with chlorogenic acid decreased the expression of IL-6, IL-17, and TNF-α.	[35]
Fibrosarcoma	In vivo	Adult albino mice	1.030, 2.060 and 4.120 mM in drinking water administered daily (8 weeks)	In caffeine-treated mice, tumor incidence, size, and growth rate decreased with the increase in caffeine concentration. In addition, caffeine-treated mice had a higher percentage of cytotoxic T cells and higher TNF-α and IFN-γ levels.	[16]
Fibrosarcoma	In vivo	Adult Syrian golden hamsters	100 mg/kg/day, intragastrical administration; treatment started 3 days before inoculation with sarcoma cells and continued for 14 days	Administration of metformin and caffeine resulted in inhibition of fibrosarcoma growth.	[36]
Melanoma	In vivo	Albino mice and C57BL/6J mice	4.120 mM daily in drinking water (3 or 6 weeks)	In the carcinogen-induced tumor model, the groups treated with caffeine alone decreased the tumor growth rate from 5.3 mm^2/day to 2.6 mm^2/day. The combination with anti-PD1 led to a more pronounced decrease (0.9 mm^2/day).	[37]
Osteosarcoma	In vivo	Athymic nu/nu nude mice	100 kg/kg/day, orally administered for 14 consecutive days	The osteosarcoma mice model (patient-derived orthotopic xenograft) treated with cisplatinum + oral recombinant methioninase + caffeine, showed the most marked decrease in comparison to the other groups.	[38]
Synovial sarcoma	In vivo	Athymic nu/nu nude mice	100 mg/kg/day, orally administered for 14 consecutive days	The combination of oral recombinant methioninase and caffeine reduced tumor volume.	[27]

IC_{50}, half-maximal inhibitory concentration; NADH, nicotinamide adenine dinucleotide; MTT assay, (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay; Anti-PD1, anti-Programmed Cell Death Protein 1; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma; G6PDH, glucose-6-phosphate dehydrogenase; NADP+, nicotinamide adenine dinucleotide phosphate; IP, intraperitoneally.

Understanding the effects of caffeine on cancer and the mechanisms underlying this effect is of extreme importance. **Table 1** summarizes the most recent (from 2018) works on this topic. These studies also contribute to determining the necessary caffeine quantities to achieve a therapeutic effect and to ensure the safe use of caffeine.

2. Anti-Inflammatory and Immunomodulation

2.1. Autoimmune Diseases and Immunomodulation

Inflammation is usually caused by infection or damage to a tissue [39]. Caffeine has the ability to exert modulation on the immune system. The immune response can be divided into two types: (i) innate and (ii) adaptive immunity [40]. Acute inflammation is a mechanism of innate immunity, whereas chronic inflammation usually contributes to the development of various diseases, such as metabolic disorders, neurodegenerative diseases, and even cancers [41][42]. The effect of caffeine on the innate immune system is related to the reduction in macrophage, neutrophil, and monocyte chemotaxis [43][44]. As for adaptive immunity, the effect of caffeine is due to the inhibition of Th1 and Th2 cell proliferation, as well as to the alteration of B cell function and the consequent reduction in antibody production [44][45][46][47]. Several authors, such as Horrigan et al., Açıkalın et al., and Al Reef et al., already reviewed, in depth, the impact of caffeine on the immune system and its capacity to alleviate autoimmune diseases [43][48][49].

Considering the immunomodulatory effects of caffeine, Wang et al. evaluated its effects on multiple sclerosis. Experimental autoimmune encephalomyelitis is the standard animal model for multiple sclerosis. After inducing the disease in C57BL/6 mice, these were treated with caffeine (10, 20, or 30 mg/kg/day) in drinking water. The results showed that caffeine could reduce inflammatory cell infiltration, the degree of demyelination, and microglial in vivo. It also reduced NLRP3 and p62 protein levels. In vitro assays indicated that caffeine promoted autophagy [50]. In another study, Ghaffary et al. evaluated the potential of mesenchymal stem cells to reduce the severity of rheumatoid arthritis. Wistar rats were treated with mesenchymal stem cells that had previously been incubated with various concentrations of caffeine. The results showed that the rats treated with mesenchymal stem cells, previously treated with 0.5 mM of caffeine, presented decreased disease severity and serum levels of C-reactive protein, nitric oxide, myeloperoxidase, and TNF-α. In addition, the IL-10 serum levels and the weight of the treated rats increased [51].

2.2. Ocular Diseases

Adenosine receptors are also expressed by retinal endothelial and retinal pigment epithelial (RPE) cells, as well as choroid and choroidal cells [52]. Therefore, caffeine may also have beneficial effects in ocular diseases, such as choroidal neovascularization and retinal inflammation.

Retinal inflammation is involved in ocular diseases as age-related macular degeneration (AMD) and diabetic retinopathy (DR), among others. For example, AMD is characterized by elevated vitreous levels of IL-1β [53] and plasmatic tumor necrosis receptor 2 (TNF-R2) and low levels of brain-derived neurotrophic factor (BDNF) in the aqueous humor, which negatively affect photoreceptor and retinal ganglion cells' survival [54]. Conti et al. demonstrated that caffeine has an anti-inflammatory effect in RPE cells, decreasing the expression of IL-1β, IL-6, and TNF-α, as well as the nuclear translocation of nuclear factor kappa B (NF-κB). In addition, the topical instillation of caffeine in an ischemia-reperfusion injury mice model was shown to restore physiological BDNF levels and reduce the mRNA levels of IL-6 in the retina, demonstrating its potential for the treatment of retinal inflammation and degeneration [55]. The effect of caffeine on choroidal adenosine receptors, the reduction in cell migration to the injured area, and angiogenesis demonstrate the importance of caffeine in attenuating choroidal neovascularization [52]. Despite the potential of caffeine in the management of such ocular conditions, the available studies are still scarce.

2.3. Respiratory Diseases

Currently, there are respiratory diseases for which caffeine is used as a clinical treatment, namely, premature infant diseases such as apnea and bronchopulmonary dysplasia (BPD). BPD is a common neonatal pulmonary complication with a prevalence of 45% in preterm infants [56]. BPD is associated with a nonspecific inflammatory response involving the activation of Toll-like receptors (TLRs), NOD-like receptors (NLRs), and increased levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, IL-18, TNFα) [57]. In addition, NLR3 (NOD-, LRR-, and pyrin domain-containing protein 3), a key player in

the pathogenesis of BPD, is responsible for the release of pro-inflammatory cytokines (IL-1β and IL-18) and alveolar cell death through various mechanisms [58][59]. Caffeine is the most commonly used medication for extreme prematurity (less than 28 weeks) and is also very commonly prescribed for very early preterm birth (28 to 32 weeks) [60]. As clinically shown, the early initiation of caffeine treatment (5 and 10 mg/kg/day) is important to achieve a successful outcome. Early treatment significantly reduced BPD incidence and mortality in low-birth-weight neonates [61]. Despite the use of caffeine and its clear benefits, the mechanisms behind the clinical benefits in these diseases are not fully understood.

In vitro studies showed that the treatment of lipopolysaccharide (LPS)-induced macrophages with caffeine caused a reduction in caspase-1 expression and the inhibition of the NLRP3 inflammasome, demonstrating its potential effect on this important target. Moreover, in vivo, the treatment of newborn mice with hypoxia-induced lung injury with caffeine was shown to significantly increase A2a receptor expression and inhibit the NLRP3 inflammasome protein and NF-κB pathway in the lung. The effect of caffeine on these key regulators attenuated inflammatory infiltration, reduced oxidative stress, decreased alveolar cell death, and promoted alveolar development [62]. Similar results were also observed in another study; specifically, caffeine caused a decrease in NF-κB and pro-inflammatory factor levels, increased the expression of A1, A2a, and A2b receptors, and decreased cell death in the lung [63].

Table 2 summarizes recent research findings on the anti-inflammatory effects of caffeine and its effects on autoimmune diseases.

Table 2. Overview of the latest research regarding caffeine anti-inflammatory activity and impact on the immune system.

Target/Disease	Study Type	Model	Caffeine Exposure	Result	Reference
Anti-inflammatory effect and immunomodulation	**In vitro**	**Human peripheral blood mononuclear cells**	**1.16 mM**	**Caffeine reduced the levels of several cytokines (IL-8, MIP-1β, IL-6, IFN-γ, GM-CSF, TNF-α, IL-2, IL-4, MCP-1, and IL-10. It also inhibited STAT1 signaling.**	**[64]**
Bronchopulmonary dysplasia	**In vitro**	**THP-1-derived macrophages**	**100–800 µM**	**There was a decrease in NLRP3 inflammasome activation, ASC speck formation, and caspase 1 cleavage. In addition, IL-1β and IL-18 secretion decreased, as well as the phosphorylation of MAPK and NF-kB pathway members.**	**[65]**
Immunomodulation	**In vitro**	**Monocytes and macrophage**	**300–1000 µM**	**Caffeine suppressed TNF-α and Akt signaling in both LPS-activated macrophage subtypes, inhibited STAT/IL-10 signaling in macrophage colony-stimulating factor, and significantly increased the expression of A2a and downregulated mTOR phosphorylation in M-macrophages.**	**[66]**
Immunomodulation	**In vitro**	**Mesenchymal stem cells and neutrophiles**	**0.1–1 mM**	**Caffeine-treated mesenchymal stem cells produced fewer reactive oxygen species and increased phagocytosis of neutrophils co-cultured with mesenchymal stem cells.**	**[67]**
Immunomodulation	**In vitro**	**Mesenchymal stem cells and neutrophiles**	**0.1–1 mM**	**Caffeine treatment increased the viability of co-cultured neutrophils.**	**[68]**

Target/Disease	Study Type	Model	Caffeine Exposure	Result	Reference
Melanoma	In vitro and in silico	Mel1 and Mel3 cells	1 and 2 mM	After caffeine treatment, there was a decrease in the levels of IL-1β, IP-10, macrophage inflammatory protein 1-α, and CCL4. On the other hand, the expression of regulated and normal T cells decreased in the Mel3 cell line.	[69]
Autoimmune encephalomyelitis	In vitro and in vivo	Primary microglia and BV2 cells C57BL/6 mice were immunized to induce autoimmune encephalomyelitis	2 mM (in vitro) 10, 20 and 30 mg/kg/day in drinking water (30 days) after immunization with $MOG_{35–55}$	Caffeine decreased clinical score, inflammatory cell infiltration degree of the demyelination, and microglia stimulation in mice. In addition, it increased LC3-II/LC3-I levels and decreased NLRP3 and P62 levels.	[50]
Choroidal neovascularization	In vitro and in vivo	Laser photocoagulation C57BL/6j mice model	200, 400 μM (in vitro); before laser photocoagulation (day 9): 20 mg/kg at day 0 and 10 mg/kg at day 1–4 and day 7 to 8; after laser photocoagulation: 10 mg/kg for 2 weeks (excluding weekends)	Significantly reduced the migration of retinal and choroidal endothelial cells (in vitro). Decreased choroidal neovascularization and inflammatory (mononuclear phagocytes) cells recruitment to the lesion area.	[52]
Depression	In vitro and in vivo	CBA × C57BL/6 F1 mice and syngeneic splenocytes	Transplantation (IV injection) with 15×10^6 splenocytes previously treated with 100 μg of caffeine for 25 min	Immune cells treated with caffeine and transplanted into depressive-like mice resulted in an increase in neuronal density and anti-inflammatory cytokines (IL-10 and IL-4) and a decrease in proinflammatory cytokines (IL-1β, INF-γ, and TNF-α).	[70]
Infection	In vitro and in vivo	Peritoneal macrophages and Swiss mice infected with *L. Monocytogenes*	0.0257–25.7 μM (in vitro) 0.05, 0.5, 5 mg/Kg of caffeine IV injected 30 min after mice infection	In mice, the leucocyte infiltration in the peritoneal cavity decreased after caffeine treatment. In addition, mRNA expression of IL-1β, IL-6, and the enzyme inducible nitric oxide synthase were decreased, whereas IL-10 was increased.	[71]
Immunological and metabolic anomalies in obesity	In vitro and in vivo	Male Sprague-Dawley rat, RAW 264.7 macrophage and HepG2 cells	50, 100, 150 mM (in vitro*)* High-fat-diet (6 weeks) induced hepatic steatosis mice were treated with 20 mg/kg/day by oral gavage (6 weeks)	In caffeine-treated mice, the profiles of TNF−α, MCP-1, IL-6, intercellular adhesion molecule, and nitrite were suppressed. In addition, live white adipose tissue and muscle macrophages and their cytokine levels also decreased.	[72]
Retinal inflammation	In vitro and in vivo	Ischemia reperfusion (I/R) injury mice model	1–100 μM (in vitro); 10 μL at 97.8 mM instilled 60 min before and after I/R reperfusion, twice a day for 72 h	Caffeine reduced the secretion of IL-1β, IL-6, and TNF-α and restored the integrity of retinal cell monolayer (in vitro). Instilled caffeine reduced IL-6 mRNA levels and maintained BDNF physiological levels in the retina.	[55]

Target/Disease	Study Type	Model	Caffeine Exposure	Result	Reference
Rheumatoid arthritis	In vitro and in vivo	Mesenchymal stem cells and Wistar rats	0–1 mM (in vitro); 14 days after rheumatoid arthritis induction, mice were injected IP with 2×10^6 cells previously treated with 0.5 mM caffeine for 48 h	Caffeine at a concentration of 0.5 mM promoted lower levels of cytokines, such as IFN-γ, IL-6, and IL-1β, and higher levels of IDO and TGF-β. In addition, cells treated with caffeine diminished the severity of rheumatoid arthritis in vivo and caused a decrease in serum levels of C-reactive protein, nitric oxide, myeloperoxidase, and TNF-α.	[51]
Cognitive impairment	In vivo	BALB/c mice	0.025, 0.05, 0.1 mg of caffeine intranasally administered (10 µL) 1 day before ischemia-induced cognitive impairment in mice, and the next 7 consecutive days	Caffeine improved the behavior outcomes of ischemic mice and reduced the expression of proinflammatory biomarkers (TNF-α, IL-6) and increased the levels of anti-inflammatory cytokines (IL-10).	[73]
Hepatic fibrosis—antioxidant and anti-inflammatory	In vivo	Hepatic fibrosis Sprague Dawley rats	50 mg/kg/day orally administered (8 weeks)	Decreased fibrosis and necro-inflammation; decreased LPAR1, TGF-β1, CTGF, α-SMA, and LPAR1 expression; improved liver function.	[74]
Hydrocephalus	In vivo	Kaolin-induced hydrocephalus mice neonates	50 mg/kg/day of caffeine were administered to dams by gavage or water (21 days) and lactated the neonates	Administration of caffeine to dams reduced cell death and increased the neurons dendritic arborization in the sensorimotor cortex and striatum of the mice neonates and improved hydrocephalic deficits and behavioral development.	[75]
Immunomodulation and anti-inflammatory effect	In vivo	Nile tilapia	Diet containing 5 and 8% *w/w* (21 days)	Caffeine supplemented diet prevented alterations caused by hypoxia, such as ATP hydrolysis and consequent accumulation in the extracellular environment.	[76]
Inflammation and adenosinergic system in cerebellum	In vivo	Ethanol-induced inflammation in Wistar and UChB rats	15.4 mM/day in 10% ethanol solution (55 days)	Caffeine reduced gene expression of A1 and A2a receptors and increased and reduced A1 and A2a protein levels, respectively, in the cerebellum. Caffeine also attenuated the inflammation, demonstrating a neuroprotective role.	[77]
Neuroinflammation	In vivo	Sprague Dawley rats	60 mg/kg/day administered orally by gavage (2 days)	Caffeine/modafinil increased the levels of anti-inflammatory (IL-4 and IL-10) and decreased proinflammatory (TNF-α, IL-1β) cytokines in the hippocampus. Treatment decreased microglial immunoreactivity and improved inflammatory response and anxious behavior.	[78]

Target/Disease	Study Type	Model	Caffeine Exposure	Result	Reference
Neurotoxicity	In vivo	Tramadol-induced damage in cerebellum rat model	37.5 mg/kg/day administered orally by gavage (21 days)	Caffeine upregulated autophagy-related genes and reduced the expression of inflammatory and apoptosis markers, demonstrating neuroprotective effects in the cerebellum.	[79]
Neurotoxicity—antioxidant and anti-inflammatory	In vivo	Albino rats	20 mg/kg/day IP injected (30 days)	Caffeine reduced oxidative stress and restored TNF-α levels in cerebral tissues.	[80]
Oxygen-induced inflammatory lung injury	In vivo	Neonatal rats	10 mg/kg IP injected every 48h (15 days)	Under hyperoxia, caffeine decreased pro-inflammatory mediators (TNF-α, IL-1α, IL-1β, IFN-γ) and NF-kB, and decreased infiltrating cells in the lung. Opposite effects were observed in normoxiaconditions.	[63]
Dental pain	Clinical Trial	Patients with acute postoperative dental pain	100 mg (single dose)	Caffeine improved the effect of ibuprofen in the treatment of moderate postoperative dental pain.	[81]

IL, interleukin; TNF-*α*, tumor necrosis factor alpha; IFN-*γ*, interferon gamma; MCP-1 (monocyte chemoattractant protein-1); STAT1, Signal Transducer and Activator of Transcription 1; Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; mTOR, mammalian target of rapamycin; NLRP3, NLR family pyrin-domain-containing 3; NF-*κ*B, nuclear factor-*κ*B MAPK, mitogen-activated protein kinase; IP-10, interferon gamma-induced protein 10; CCL4, CC motif chemokine ligand 4; TGF-*β*, transforming growth factor beta; CTGF, connective tissue growth factor; *α*-SMA, alpha smooth muscle actin; LPAR1, lysophosphatidic acid receptor 1; LPS, lipopolysaccharide; M-MFs, inflammation-resolving macrophages; GM-MFs, inflammation-promoting macrophages; NF*κ*B1, nuclear factor kappa B subunit 1; HMGB1, high mobility group box 1 protein; BDNF, brain-derived growth factor.

3. Neurodegenerative Diseases

By 2050, the number of dementia cases worldwide is estimated to be 36.5 million [82]. There are several neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and multiple sclerosis [83][84]. For example, Parkinson's disease is triggered by the loss of neurons, which leads to a decrease in dopamine levels. In Alzheimer's disease, there is a deposition of extracellular deposits of amyloid-beta peptides and neurofibrillary tangles [85][86].

Caffeine is considered the most widely consumed psychoactive stimulant in the world. This natural compound is able to cross the blood–brain barrier [87][88] and, according to the literature, may exert a stimulant effect on the central nervous system by modulating several molecular targets, such as the (i) antagonism of adenosine receptors, (ii) promotion of intracellular calcium mobilization, (iii) inhibition of phosphodiesterase, and (iv) inhibition of $GABA_A$ receptors. However, except for the blockade of adenosine receptors and consequent inhibition of neurotransmitter-induced signaling pathways, the other mechanisms only exert their effects at toxic concentrations of caffeine [87][89][90][91]. Recently, Ruggiero et al. reviewed the available literature on the protective effects of caffeine in various neurodegenerative diseases [92]. Among these studies, some emphasized the neuroprotective role of caffeine. For example, Manolo et al. showed that caffeine, at a concentration of 10 mM, is able to protect 96% of the dopaminergic neurons. The co-administration of olanzapine and caffeine did not result in neuroprotection, implying that both dopamine D2-like and A2a receptors are required for neuroprotection [93]. In an in silico study of Parkinson's disease, the authors demonstrated that caffeine has the ability to bind to both wild-type and mutant parkin protein [94]. The mutation of parkin protein is the most common cause of Parkinson's disease, as is the abnormal secretion and accumulation of α-synuclein [95][96]. This last part was detected in the following in vivo studies. Luan et al. investigated whether caffeine could protect against mutant α-synuclein-induced toxicity. Exposing mice to 1 g/L of caffeine in drinking water attenuated apoptotic neuronal cell death as well as microglia and astroglia reactivation, culminating in synucleinopathy [97]. In a similar study, Yan et al. investigated synergetic neuroprotection between caffeine and eicosanoyl-5-hydroxytryptamide. Both compounds are present in coffee and showed no effect at subtherapeutic doses, whereas their combination reduced the accumulation of phosphorylated α-synuclein, and maintained neuronal integrity and function [98].

4. Cardiovascular Diseases

Cardiovascular disease (CVD), the leading cause of mortality, accounted for 17.8 million deaths worldwide between 1980 and 2017 [99]. By 2030, an estimated 23.6 million people per year will die due to CVD. Caffeine intake, particularly through the consumption of coffee, tea, and other products, has shown various cardiovascular effects. Turnbull et al. reviewed more than 300 studies regarding the effects of caffeine on cardiovascular health, published from the late 1980s to 2017. Overall, the results suggest that caffeine consumption does not increase the risk of CVD and may have a protective effect against this group of diseases [100]. However, recent studies on this topic have shown that high caffeine consumption may have the opposite effect.

A study of 347,077 people (UK Biobank) concluded that coffee consumption may modestly increase the risk of cardiovascular disease. A nonlinear association was found between long-term coffee consumption and cardiovascular disease. Individuals who consumed coffee in high doses (>6 cups/day, >450 mg caffeine/day) were more likely to develop cardiovascular disease (22%) than those who consumed less coffee (1–2 cups/day or 75–150 mg caffeine/day) [101]. In addition, the authors examined the association between coffee consumption, plasma lipids, and CVD risk in 362,571 individuals (UK Biobank). The results showed that high coffee consumption (>6 cups/day) may increase CVD risk by increasing the levels of low-density lipoprotein cholesterol (LDL-C), total cholesterol (total-C), and apolipoprotein B (ApoB) [102].

However, other studies have reported the potential beneficial effects of moderate coffee consumption, in line with Turnbull et al.'s literature review [100]. For instance, a study involving 20,487 Italian participants concluded that moderate coffee consumption (3–4 cups/day) was associated with a low risk of CVD-related mortality. In addition, an inverse correlation was found between NT-proBNP levels (N-terminal fragment of the B-type natriuretic peptide, which is associated with higher stroke risk) and coffee consumption [103]. Similarly, a study of more than 500,000 participants in England reported that a caffeine intake of 121–182 mg/day from coffee (2–3 cups/day) or tea (4–6 cups/day) was associated with a low risk of coronary artery disease [104]. In addition, a US follow-up study of 23,878 participants over 16 years found that the daily caffeine consumption of about 100–200 mg or >200 mg is associated with a lower risk of CVD mortality [105]. An inverse association between coffee consumption and CVD risk factors (blood pressure and arterial stiffness) was also observed in another study, showing the beneficial effect of moderate coffee consumption [106]. A similar association was observed concerning coffee consumption and hypertension risk [107].

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